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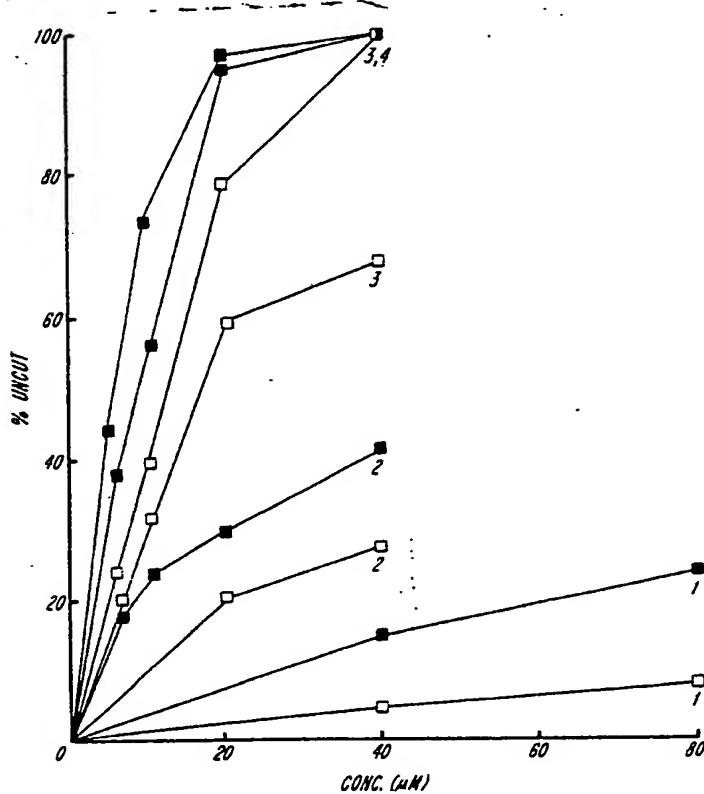
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(54) Title: BISPLATINUM COMPLEXES AS CHEMOTHERAPEUTIC AGENTS

(57) Abstract

A bis-platinum complex having the structure (I), wherein X and Y are the same or different ligands and are halide, sulphate, phosphate, nitrate, carboxylate, substituted carboxylate or dicarboxylate. B and C are the same or different and are primary or secondary amines, or pyridine type nitrogens. A is a diamine or polyamine wherein the primary amine N atoms are coordinated to the Pt atom such that platinum is present as Pt^{2+} . The complexes are useful in the inhibition of tumors.



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BISPLATINUM COMPLEXES AS CHEMOTHERAPEUTIC AGENTS
BACKGROUND OF THE INVENTION

The present invention relates to novel bis-platinum complexes and to pharmaceutical compositions containing them.

5 While cisplatin is widely used because of its antitumor activity, the search has continued for more powerful agents.

10 U.S. Patent No. 4,225,529, discloses a cis coordinated compound of platinum having four ligands. (X, Y, A & B). The ligands X and Y are the same or different ligands selected from the group comprising a halide, sulphate, phosphate, nitrate, carboxylate, or substituted carboxylate and water. A and B are the same or different straight chain amines coordinated to the Pt through their N atoms, such that the platinum is represented by Pt^{2+} . The "diaquo compound" is formed by a literature method described in the Indian Journal of Chemistry, 8, 143. (1970).

15 20 U.S. Patent No. 4,250,189, discloses platinum coordinated compounds of Pt^{2+} or Pt^{4+} . The Pt^{2+} compounds have four ligands, two of the ligands (X and Y) being selected from the group sulphate, phosphate, nitrate, carboxylate, or substituted carboxylate and water. The other two ligands are amines linked for example by an alkylene. The compound is contemplated 25 for pharmaceutical use with a carrier.

30 U.S. Patent No. 4,533,502, discloses platinum (II) compounds and their method of preparation. The starting compound is a cis - $[\text{PtL}_2\text{-I}_2]$ compound where L is an amine bonded to the Pt through the nitrogen and I is iodine. The starting compound is converted into cis-platinum (II) compounds similar to those in U.S. Patent No. 4,225,529 above or a complex where two platinum (II) units are bridged by tetracarboxylate and

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each of the platinum (II) atoms are bonded to two of the carboxylate groups of the tetracarboxylate.

5 U.S. Patent No. 4,565,884, describes a bis-platinum complex. The complex is linked by a central ligand with two pairs of acidic groups which could be carboxylates, sulphonates or phosphonates. The acids may be aromatic ring systems, alkyl cyclic ring systems or suitable aliphatic groups.

10 U.S. Patent No. 4,571,335, discloses cis platinum (II) compounds that are usable for inhibiting herpes virus where the ligands include amines, dicarboxylic acids, and sulphonates.

15 The patents noted above discuss various Pt (II) and Pt (IV) compounds which have been found to have antitumor activity or pharmaceutical applications. The majority of these compounds are of the general formula $cis-[PtLL'X_2]$ or $cis-[PtLL'(X_2)(Y_2)]$ for the Pt (II) and Pt (IV) forming complexes, respectively. L normally represents amine ligands where X is normally a halogen and Y is normally hydroxy. Those bis-platinum 20 complexes prepared in the patents above were linked through carboxylate bridges. The carboxylate linkage merely serves as a temporary carrier vehicle. Upon administration in pharmaceutical applications, such complexes undergo rapid hydrolysis to produce two cis monoplatinum moieties which are delivered to the active site. There is no recognition in the art of a 25 pharmaceutically active form of a bis-diplatinum complex which is delivered as an intact bis complex to the active site.

30 Accordingly, it is an object of this invention to produce a stable bis-platinum complex for antitumor and pharmaceutical applications, the complex being resistant to chemical breakdown prior to engaging 35 in its pharmaceutical function.

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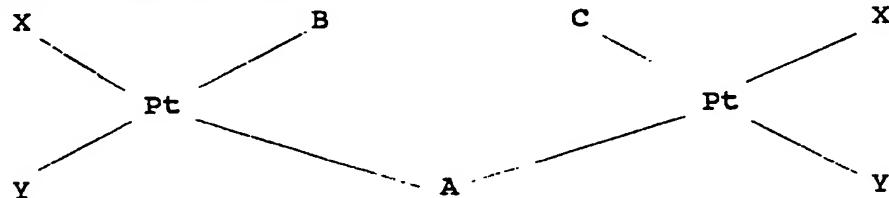
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It is a further object of the present invention to produce an improved coordinated platinum complex, the complex, exhibiting increased tumor inhibition.

5 A still further object is to provide a bis-coordinated platinum complex capable of being formulated for use in pharmaceutical functions.

SUMMARY OF THE INVENTION

10 The present invention is a bis-platinum complex having the structure:



15 wherein X and Y are the same or different ligands and are halide, sulphate, phosphate, nitrate, carboxylate, substituted carboxylate or dicarboxylate. B and C are the same or different and are primary or secondary amines, or pyridine type nitrogens. A is a diamine or polyamine wherein the primary amine N atoms are coordinated to the Pt atom such that platinum is present as Pt^{2+} .

20 BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a graph illustrating inhibition of restriction enzymes Bam HI and EcoRI by complexes of the present invention versus inhibition by cisplatin.

DETAILED DESCRIPTION OF THE INVENTION

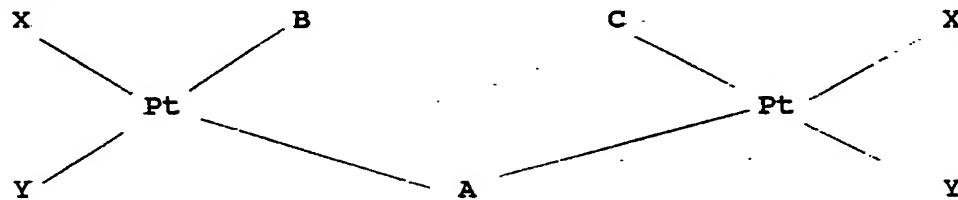
25 The present invention relates to novel bis platinum (II & IV) complexes and methods for preparing such complexes.

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According to a first aspect of the invention, there is obtained a bis platinum complex having the general structure



5 where X and Y are monodentate ligands or are combined as a bidentate ligand. B and C are the same or different amines, or pyridine type nitrogens. The bridging ligand A is a diamine or a polyamine.

10 X and Y when combined to form a bidentate ligand can comprise a dicarboxylate bidentate ligand, which may be substituted if desired. The dicarboxylates may be illustrated by the formula:



15 wherein R¹ and R² are the same or different, and are hydrogen, straight or branched alkyl of 1-5 carbon atoms, or hydroxy substituted alkyl, and k and 1 are the same or different and are an integer between 0 and 4, inclusive. Fused rings such as 1,1-cyclobutanedicarboxylate (CBDCA) are also useful. Preferred dicarboxylates are oxalate, malonate, or malonate substituted by methyl or hydroxyethyl.

20 When X and Y are represented by monodentate ligands they may be the same or different and may be halide, sulphate, phosphate, nitrate, carboxylate, or substituted carboxylate.

25 Where the X or Y groups are carboxylates or substituted carboxylates, they may be represented by the formula



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wherein m is an integer from 0 to 5, inclusive. The R^3 groups may be the same or different and may be hydrogen, substituted or unsubstituted straight or branched alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl, and cycloalkenyl, halogen, pseudohalogen, hydroxy, carbonyl, formyl, nitro, amido, amino, alkoxy, aryloxy, and sulphonic acid salts. Furthermore, the R^3 groups can be combined so that the two R^3 groups represent a doubly bonded oxygen or sulphur.

By lower alkyl and lower alkenyl in the present specification is meant one to five carbon atoms. By cycloalkyl is meant chains of 2-6 carbon atoms. By substituted in the present specification is meant substitution with a group chosen from aryl, cycloalkyl of 2 to 6 carbon atoms, cycloalkenyl, aralkyl, halogen, pseudohalogen, hydroxy, alkoxy, acycloamino, or carboxylic acid salts or esters of one to five carbon atoms.

The term "pseudohalogen" in this specification has the meaning found on page 560 of "Advanced Inorganic Chemistry" by Cotton and Wilkinson, Interscience Publishers, 1966. The text describes a pseudohalogen as being a molecule consisting of more than two electronegative atoms which, in the free state, represent halogens. Examples of these molecules are cyanide, cyanate, thiocyanate and azide.

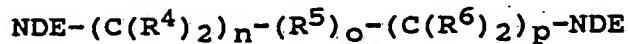
The B and C amines are the same or different and can include ammonia, branched or straight chain lower alkyl amines, aryl amines, aralkylamines, lower alkenyl amines, cycloalkyl amines, cycloalkylenyl amines, and polycyclic hydrocarbon amines. Heterocyclic amines, nucleosides, nucleotides, pyridine-type nitrogen containing compounds, or amines with hydroxy, lower alkoxy, carboxylic acid or acid ester, nitro and halo substituents can be employed.

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The bridging ligand A has the formula:



in which n and p are integers from 1 to 4, inclusive and o is 0 or 1; and the R^4 and R^6 groups are the same or different and are hydrogen, lower alkyl, aryl, cycloalkyl, cycloalkenyl, aralkyl, halogen, pseudohalogen, hydroxy, alkoxy, aryloxy, carboxylic acid ester, or carboxylic acid salt. Preferably all R^4 and R^6 groups are hydrogen.

The R^5 group is optional, and if employed is selected from alkyl, aryl (such as phenyl), amino, alkylamino, diamino of the formula:



wherein q is an integer of 1 to 4, inclusive, hydroxyalkyl, alkoxy, sulfur or oxygen.

The D and E groups are the same or different and are selected from hydrogen, lower alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, halogen, pseudohalogen, hydroxy, alkoxy, aryloxy, or sulphonic acids or salts thereof. The preferred substituent is hydrogen.

Particularly preferred A bridging ligands include straight chain diamines having the general formula:



wherein r is an integer from 2 to 12, inclusive. A second preferred embodiment contemplates the use of straight chain polyamines such as spermidine and spermine. These polyamines can be naturally occurring. Such naturally occurring polyamines can increase the

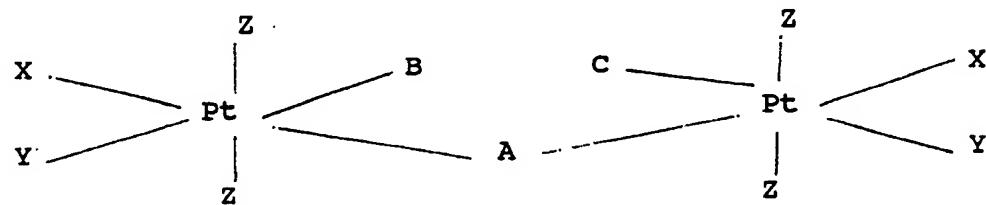
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solubility of the bis complex while simultaneously increasing the covalent binding of the complex.

In a second aspect of the invention there is provided a platinum (IV) bis complex having the structure



wherein the Z groups are the same or different and are selected from nitrate, halogen, pseudohalogen, or hydroxy, and X, Y, A, B, and C are as defined above.

The preferred anions of Z are hydroxy and chloro.

The bis platinum complexes according to the present invention are intended for pharmaceutical application. The complex is useful for the treatment of the same diseases and modalities in the same patients as cisplatin. This includes the treatment of tumors, radiation sensitization or potentiation (Douple et al, "Cisplatin, Current Status and New Developments," Eds. A.W. Prestayko, S.T. Crooke, and S.K. Carter, Academic Press, 125 (1980); Douple, Platinum Metals Rev., 29, 118 (1985)), and parasitic diseases such as sleeping sickness (Farrell et al, Biochem. Pharmacology, 33, 961 (1984)). The complexes of the present invention are administered at approximately the same dosage levels as cisplatin, while taking into account their LD₅₀ values. The complex is normally associated with a suitable pharmaceutically acceptable carrier. For example, the complex and carrier can be formulated for parenteral or oral administration by methods well known in the art.

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5 In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that these examples are intended only to be illustrative without serving as a limitation on the scope of the present invention.

10 The examples describe the preparation of the complexes by reaction of $K[PtCl_3(NH_3)]$ with the bridging ligand. The $K[PtCl_3(NH_3)]$ compound is prepared by the general method of T.S. Elleman et al, J. Amer. Chem. Soc., 80, 536 (1958). For amines other than NH_3 , i.e., $K[PtCl_3(amine)]$, the general procedure of Pasini et al, Inorg. Chim. Acta, 93, 167 (1984), incorporated herein by reference, is preferred.

15

EXAMPLES 1-10Preparation of $\left[\{PtCl_2(NH_3)\}_2H_2N(CH_2)_rNH_2\right]$ Complexes

20 $K[PtCl_3(NH_3)]$ was slurried in a methanol solution in the ratio of 536.2 mg (1.5 mmol) to 5 ml of the methanolic solution. To a methanolic suspension of $K[PtCl_3(NH_3)]$ is added a methanolic solution of the appropriate diaminoalkane (0.75 mmole in 30 millimeters). The mixture is stirred for 24 hours. The product bis complex forms an insoluble precipitate. Then the mixture is filtered using a sintered glass filter of medium porosity to obtain a creamish solid. The precipitate is washed with approximately five ml of water and twice with approximately five ml of methanol. The washed product is then dried in vacuo for approximately two hours at a temperature of

25 approximately 50-60°C.

30

The above procedure was repeated for straight chain diaminoalkanes of the general formula $[H_2N(CH_2)_rNH_2]$ with the number r being an integer of 3 to 12, inclusive.

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The complexes formed were white to cream solids. The complexes were sparingly soluble in water and alcoholic solvents and soluble in polar solvents such as dimethylsulfoxide (DMSO), dimethylformamide (DMF) and dimethylacetamide (DMA). Certain of the precipitated complexes formed by the reaction were subjected to elemental analysis. The data in Table I summarizes the results for the $[\{\text{PtCl}_2(\text{NH}_3)\}_2\text{H}_2\text{N}(\text{CH}_2)_r\text{NH}_2]$ complexes:

10

TABLE I

<u>ELEMENTAL ANALYSES</u> <u>FOUND (CALCULATED)</u>				
<u>r</u>	<u>%C</u>	<u>%H</u>	<u>%N</u>	<u>%Cl</u>
	2	4.04 (3.83)	2.34 (2.23)	8.63 (8.94)
15	3	5.60 (5.62)	2.41 (2.50)	8.68 (8.75)
	4	7.65 (7.33)	2.84 (2.75)	8.35 (8.56)
	5*	10.11 (10.28)	3.14 (3.42)	7.87 (8.00)
	6	10.15 (10.55)	2.93 (3.22)	6.68 (8.21)
	7	11.93 (12.06)	3.47 (3.44)	7.90 (8.04)
20	8	13.35 (13.52)	3.70 (3.66)	7.63 (7.88)
	9	15.58 (14.91)	4.03 (3.86)	7.37 (7.73)
	10	16.82 (16.26)	4.14 (4.06)	7.12 (7.59)
	12	19.86 (18.79)	4.60 (4.43)	7.02 (7.31)

25 *Calculated with one mole of methanol of recrystallization.

Additionally, characterization data was obtained from infrared spectra. The tests were run on KBr disks. The data obtained corresponded to that of a cis configuration of the chlorides on each platinum

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atom. Representative wavelength values of Pt-Cl coordination are 326, 318(sh)cm⁻¹, for the r=4 derivative, and 330, 310(v.b.)cm⁻¹, for the r=5 derivative. Values (in cm⁻¹) for other derivatives are 5 326, r=6; 329, r=7; 328, r=8; 328, r=9; 328, r=10; and 325, r=12.

EXAMPLES 11 and 12

10 Pt(IV) complexes were formed by oxidation with H₂O₂. The preparation was carried out by a standard procedure described by Kuroda et al, Inorg. Chem., 22, 3620 (1983), incorporated herein by reference. The Pt(II) complexes were oxidized by this standard procedure to yield a Pt(IV) complex having the general formula [{PtCl₂(OH)₂NH₃}]₂H₂N(CH₂)_rNH₂. This 15 procedure was performed on the r=5 and r=7 complexes of Examples 4 and 6 above.

Elemental analysis of these two complexes yielded the results set forth in Table II.

TABLE II

20	<u>ELEMENTAL ANALYSES</u> <u>FOUND (CALCULATED)</u>		
<u>r</u>	<u>%C</u>	<u>%H</u>	<u>%N</u>
5	8.15 (8.17)	3.25 (3.39)	7.60 (6.62)
7	10.99 (11.87)	3.66 (3.76)	7.32 (6.36)

25 The I.R. spectrographic data on these complexes were similar to that of their respective Pt(II) starting complexes, except for slightly higher values of 336 cm⁻¹ for r=5 and 331 cm⁻¹ for r=7. The 30 Pt(IV) complexes obtained from the H₂O₂ are also characterized by the presence of a broad band centered

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at approximately 540-560 5cm^{-1} . This additional band is attributable to the ν (Pt-OH).

5 The Pt(II) and Pt(IV) complexes according to the invention were tested for cytotoxicity activity against L1210 murine leukemia cells. The tests were carried out in vitro according to the procedures outlined by M.P. Hacker et al in Cancer Research, 45, 4748 (1985). The results in Table III are expressed as the ID₅₀ which represents the minimum 10 dose required to cause 50% tumor inhibition.

TABLE III

TUMOR INHIBITION DATA

	<u>r</u>	<u>ID₅₀ (g/ml)</u>
	2	> 10
15	4	1.4, 2.3
	5	2.1, 3.0 0.36 (10% DMSO)
	5 (Pt(IV))	3.2, 6.0
	7	2.8
20	7 (Pt(IV))	3.9
	8	2.6
	9	1.2
	10	1.6
	12	3.0

25 In the same system, but in a cisplatin-resistant cell line, the r = 5 derivative gave values of 4.3 and 9.3 $\mu\text{g}/\text{ml}$ and thus is considered active against this line. For comparison, cisplatin gives ID₅₀ values of 0.1-02 μg in the sensitive line and

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5-7 μ g in the resistant line, denominated L1210/DDP. Thus the approximately 50-fold resistance of cisplatin is reduced to 2-3 fold in the bisplatinum series. The Pt(IV) complexes were run in water, the Pt(II) complexes in DMSO or 10% DMSO where indicated.

10 The Pt(II) complexes were also tested against L1210 tumors in BDF₁ mice. The results of these tests are expressed in %T/C, which represents the percentage of tumor weight in treated mice versus that in control mice. Again the method of testing was in accordance with the procedure published by M.P. Hacker et al, in Cancer Research, 45, 4748 (1985). The dosages were administered intraperitoneally in a suspension of hydroxypropylcellulose (HPC). The results are

15 represented in Table IV.

TABLE IV

<u>r</u>	<u>Dose (mg/kg)</u>	<u>Schedule (days)</u>	<u>%T/C</u>
4	6.25	1, 5, 9	135
	12.5	1,5	Toxic
20	5	1,5	206 (30d)
			260 (60d)
	12.5	1,5	163

*For the r=5 derivative 1/6 survivors were found at 30 and at 60 days at the higher dose.

25 The complexes of the invention were further tested to compare their DNA binding versus that of standard cis platinum cis-[PtCl₂(NH₃)₂]. An assay was

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performed using the inhibition of restriction enzymes upon binding the complexes to linearized plasmid DNA.

The method was according to a standard procedure wherein cleavage by BamHI or Eco RI at the defined sites results in only 2 fragments per enzyme since purified linear plasmid is used. DNA (20 mg/ml) in tris Cl (100 mM)-EDTA (1mM), pH 8 was exposed to complexes (usually 100 mM) for 1 hour at 37°C, after which unbound drug was removed using a spin-column of 5 G-50 Sephadex (Pharmacia). Buffer (3.5 μ l of 0.33M tris-acetate (pH7.9), 0.66M potassium acetate, 0.10M magnesium acetate, 0.005M dithiothreitol, 1 mg/ml bovine serum albumin) and 10 units of enzyme were added to 10 eluted DNA (30 μ l). EDTA (1 μ l, 0.5M) was used to stop 15 enzyme activity after 30 min, 37°C; and tracking dye (7 μ l:0.25% bromophenol blue, 0.25% xylene cyanol, in 30% glycerol water) was added. 10 μ l of resulting 20 solution was loaded onto a 1% agarose gel, made with E buffer (0.40 M Tris, 0.005 M sodium acetate, 0.001 M EDTA, pH to 7.8 with glacial acetic acid) and subjected to horizontal electrophoresis at 25V. The slab gel was stained with aqueous 1:10000 ethidium bromide solution (1 ng/ml) and photographed under UV light with an MP-4 25 Polaroid camera.

Inhibition of restriction enzymes BamHI and Eco RI was assessed qualitatively by noting the relative proportions of bands (cleaved vs uncleaved) or quantitatively by densitometer (Kipp & Zonen DD2) scan of the negative of the recorded picture.

The results are summarized in Figure 1. 30 Complex 1 represents trans-[{PtCl₂(DMSO)}₂H₂N(CH₂)₄NH₂], Complex 2 is the standard reference cis platinum complex cisplatin, and Complexes 3 and 4 are the bis-Pt(II) complexes according to Examples 4 (r=5) and 3 35 (r=4), respectively. Complex 1 represents a trans configuration analog of Complex 4.

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5 The results signified by Figure 1 clearly demonstrate the increased inhibition of endonuclease activity of the bis complexes according to the invention as compared to a standard monoplatinum complex. Therefore, the bis complexes show significantly increased effectiveness at binding DNA.

10 The results of this test would apply equally to bisplatinum complexes linked by carboxylate bridges which merely serve to deliver two monoplatinum complexes, such as cisplatin, to the point of inhibition.

15 While the invention has been described in terms of various preferred embodiments, one skilled in the art will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims.

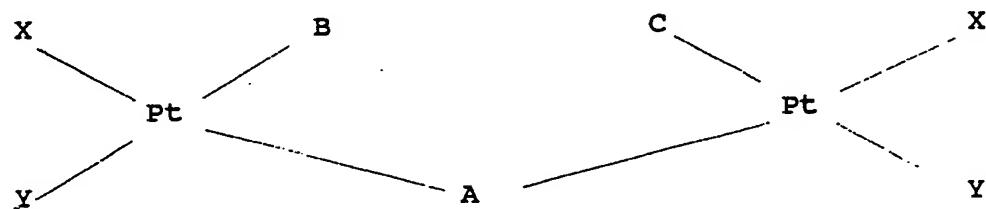
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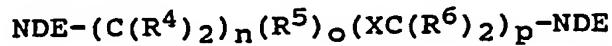
CLAIMS:

1. A bis-platinum complex having the structure:



in which X and Y are the same or different ligands and are halide, sulphate, phosphate, nitrate, carboxylate, substituted carboxylate, or dicarboxylate; B and C are the same or different groups selected from primary and secondary amines and pyridine type nitrogens; and A is a diamine or polyamine wherein the primary amine N atoms are coordinated to the Pt atom such that platinum is present as Pt^{2+} .

2. The complex according to claim 1 wherein A has the formula:



wherein n and p are integers from 1 to 4, inclusive, and o is 0 or 1; R^4 and R^6 are the same or different and are hydrogen, lower alkyl, aryl, cycloalkyl, cycloalkenyl, aralkyl, halogen, pseudohalogen, hydroxy, alkoxy, aryloxy, carboxylic ester, or carboxylic acid salt; D and E are the same or different and are hydrogen, lower alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, halogen, pseudohalogen, hydroxy, alkoxy, aryloxy, sulphonic acid, or sulphonic

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acid salt; and R5 is alkyl, aryl, amino, alkylamino, diamino of the formula:

15

 $-(\text{NH}(\text{CH}_2)_q\text{NH})-$

wherein q is an integer of 1 to 4, inclusive, hydroxyalkyl, alkoxy, sulfur or oxygen.

3. The complex of claim 2 wherein o is 0, and R⁴, R⁶, D and E are all hydrogen.

4. The complex of claim 1 wherein X and Y are all chlorine and B and C are amines.

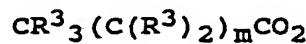
5. The complex of claim 3 wherein X and Y are all chlorine and B and C are amines.

6. The complex of claim 1 wherein A is a naturally occurring polyamine.

7. The complex of claim 6 wherein the polyamine is spermidine or spermine.

8. The complex of claim 1 wherein A is H₂N-(CH₂)_r-NH₂, and r is an integer from 2 to 12, inclusive.

9. The complex of claim 1 wherein X and Y are carboxylates or substituted carboxylates of the formula:



5 wherein m is an integer from 0 to 5, inclusive; and the R³ groups are the same or different and are hydrogen, substituted or unsubstituted straight or branched alkyl, aryl, alkaryl, carboxylic acid ester, or carboxylic acid salt.

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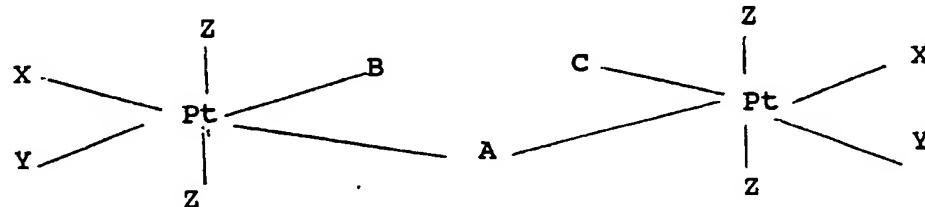
10. The complex of claim 1 wherein X and Y combine to form a dicarboxylate of the formula:



5 wherein R1 and R2 are the same or different, and are hydrogen, straight or branched alkyl or hydroxy substituted alkyl of 1-5 carbon atoms; and k and l are the same or different and are each an integer between 0 and 4, inclusive.

11. The complex of claim 10 wherein the dicarboxylate is oxalate, malonate, or malonate substituted by methyl or hydroxyethyl.

12. A bis-platinum complex having the structure:



5 in which X and Y are the same or different ligands and are halide, sulphate, phosphate, nitrate, carboxylate, substituted carboxylate, or dicarboxylate; B and C are the same or different groups selected from primary and secondary amines and pyridine type nitrogens; the Z groups are the same or different and are nitrate, halogen, pseudohalogen, or hydroxy; and A is a diamine or polyamine wherein the primary amine N atoms are coordinated to the Pt atom such that platinum is 10 present as Pt⁴⁺.

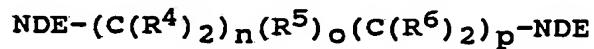
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13. The complex of claim 12 wherein Z is hydroxy or chloro.

14. The complex according to claim 12 wherein A has the formula:



5 wherein n and p are integers from 1 to 4, inclusive, and o is 0 or 1; R⁴ and R⁶ are the same or different and are hydrogen, lower alkyl, aryl, alkaryl, cycloalkyl, cycloalkenyl, aralkyl, halogen, pseudohalogen, hydroxy, alkoxy, aryloxy, carboxylic ester, or carboxylic acid salt and are the same or different and are hydrogen, lower alkyl, aryl, alkaryl, 10 aralkyl, alkenyl, cycloalkyl, cycloalkenyl, halogen, pseudohalogen, hydroxy, alkoxy, aryloxy, sulphonic acid, or sulphonic acid salt, and R⁵ is alkyl, aryl, amino, alkylamino, diamino of the formula:



wherein q is an integer of 1 to 4 inclusive, hydroxyalkyl, alkoxy, sulfur or oxygen.

15. The complex of claim 13 wherein o is 0, and R⁴, R⁶, D and E are all hydrogen.

16. The complex of claim 12 wherein X and Y are all chlorine and B and C are amines.

17. The complex of claim 14 wherein X and Y are all chlorine and B and C are amines.

18. The complex of claim 12 wherein A is a naturally occurring polyamine.

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19. The complex of claim 18 wherein the polyamine is spermidine or spermine.

20. The complex of claim 12 wherein A is $\text{H}_2\text{N}-(\text{CH}_2)_r-\text{NH}_2$, and r is an integer from 2 to 12, inclusive.

21. A pharmaceutical composition comprising an effective amount of a complex according to claim 1 in a pharmaceutically acceptable carrier.

22. A method of inhibiting tumor growth in a mammal comprising the administration to the mammal of a tumorinhibiting amount of a complex of claim 1.

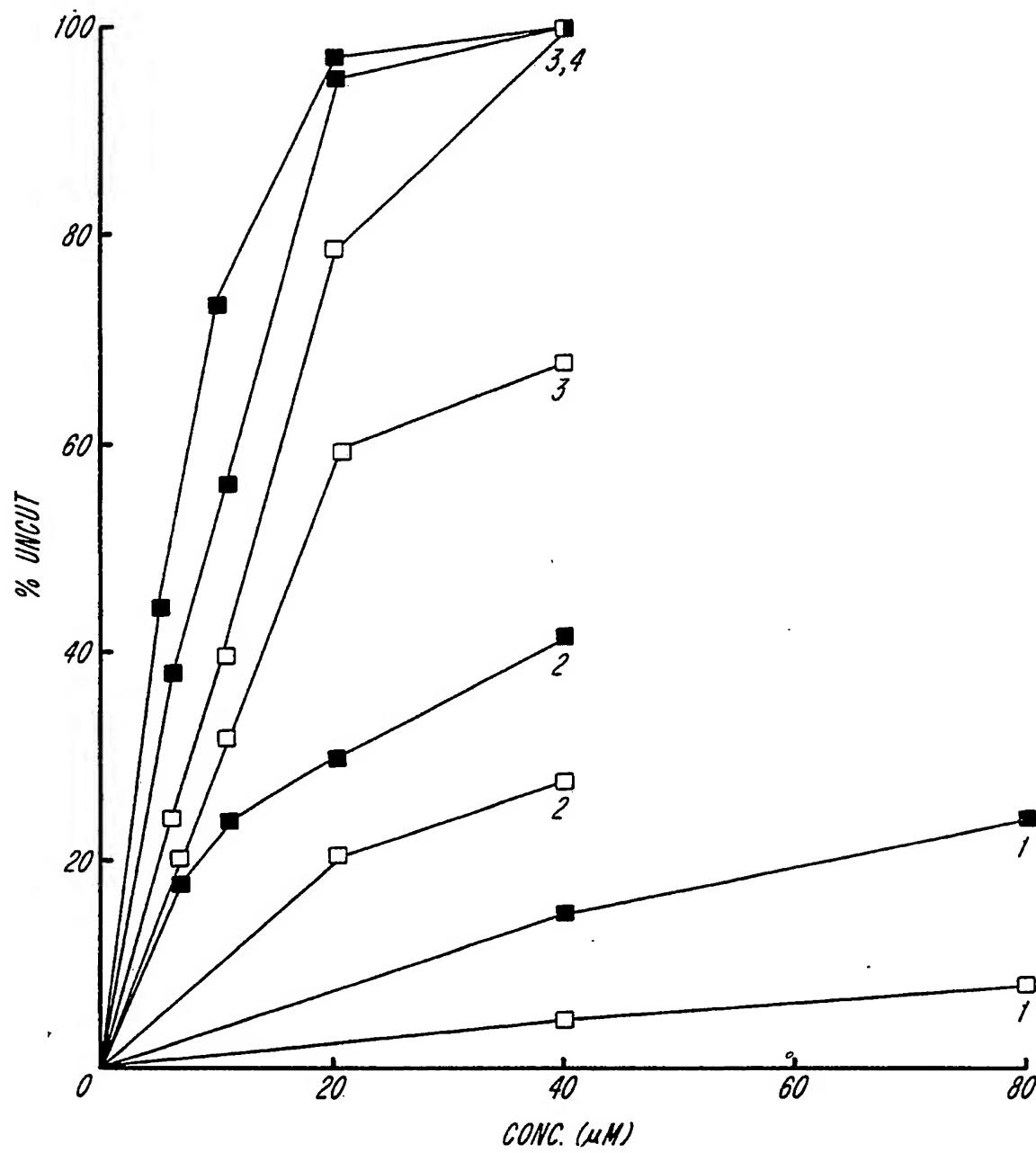
23. A pharmaceutical composition comprising an effective amount of a complex according to claim 12 in a pharmaceutically acceptable carrier.

24. A method of inhibiting tumor growth in a mammal comprising the administration to the mammal of a tumorinhibiting amount of a complex of claim 12.

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FIG. 1

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No PCT/US87/01738

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³

According to International Patent Classification (IPC) or to both National Classification and IPC
 IPC (4) : C07F 15/00; A61K 33/24

II. FIELDS SEARCHED

Minimum Documentation Searched ⁴

Classification System	Classification Symbols
U.S.	556/24 514/492 556/137

Documentation Searched other than Minimum Documentation
 to the Extent that such Documents are Included in the Fields Searched ⁵

CHEMICAL ABSTRACTS

III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴

Category ⁶	Citation of Document, ¹⁰ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X	DE, A, 3,432,320, (KOLAR ET AL) Published 13 March 1986.	1,6,9-11, 21 and 22
X	Chemical Abstracts, Vol. 87, No. 5, 01 August 1977, p. 23, Abstract No. 33558n, TSOU ET AL., "Spermine-Platinum (II) Chloride as a Potential Anti-tumor Agent".	1-7,21 and 22
A	U.S., A, 4,565,884, (ANDRULIS ET AL) Published 21 January 1986.	1-24

- Special categories of cited documents: ¹⁰
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search ⁹

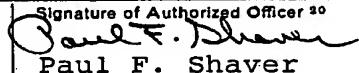
25 SEPTEMBER 1987

Date of Mailing of this International Search Report ⁹

14 OCT 1987

International Searching Authority ¹

ISA/US

Signature of Authorized Officer ¹⁰

 Paul F. Shaver